REMARKS

Claims 1, 86-90, 92-99, 101, 104-106, and 108 are pending. Claims 1 and 98 have been amended. No claims have been canceled or added. Accordingly, upon entry of the amendment, claims 1, 86-90, 92-99, 101, 104-106, and 108 will be pending.

Claim 1 has been amended to more clearly define the polypeptide administered in accordance with the claimed method as comprising a cytoplasmic binding domain of a β integrin subunit for ERK2 MAP kinase or in which the amino acid sequence of the binding domain has been modified. Additionally, the polypeptide is now defined as having a length of at least 10 amino acids, and the modified form of the binding domain as having at least 80% sequence identity with the binding domain. Moreover, claim 1 now specifically defines the ERK2 MAP kinase as being expressed by the cancer cells. In addition, claim 1 has been amended to define the respective amino acid sequences comprising the binding domains of the β2, β3, β5 and β6 integrin subunits for the ERK2 MAP kinase. Claim 98 has been amended to define the polypeptide as being up to 35 amino acids in length.

Support for the amendments to claim 1 and 98 may be found throughout the specification and claims as originally filed. For example, support for the polypeptide having a length of at least 10 amino acids is found in the specification at page 15, lines 6 – 11 and in particular, lines 10 – 11. Additional support may also be found at, for example, page 18, line 17 to page 19, line 3, which exemplifies the provision of peptides of the recited length, and particularly, page 18, line 27 to page 19, line 3, which specifically provides for peptides having a length of at least 10 amino acids. Moreover, attention is also drawn to the disclosure at page 15, lines17 – 26 of the specification which provides for various peptide lengths comprising the binding domain for the MAP kinase. Support for the amino acid sequences comprising the binding domains of the β2, β3, β5 and β6 integrin subunits for the ERK2 MAP kinase may be found at, for example, page 8, lines 7 – 13, page 18, lines 17 – 26, and page 27, lines 26 – 32. Applicant respectfully submits that no new matter has been added by the amendments.

Election/Restriction

The Applicant again reiterates the submissions made in response to the previously raised Restriction Requirement. As described in greater detail below, whilst claim 1 as now amended provides for the β integrin subunit to be selected from the group consisting of β2, β3, β5 and β6, which are all members of the same class of integrin subunits with a binding domain for ERK2 MAP kinase that has an intervening linker region joining opposite end regions of the binding domain together that is non-essential for the binding of ERK2 (and so can be deleted). Moreover, the β integrin subunit is not expressed by the cells treated with the polypeptide. Hence, the respective β integrin binding domains and the modified forms thereof provided for by claim 1 of the instant application simply constitute alternatives of the polypeptides/peptides that may be utilized within the over-arching single concept of the method now claimed.

Rejections Under 35 U.S.C. § 112, 1st Paragraph

The Examiner rejects claims 1, 86-90, 92-99, 101, 104-106, and 108 under 35 U.S.C. § 112, 1st paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner has stated that the claims do not recite the sequences of β2, β3, β5, and β6 binding domains for Erk2.

Applicant respectfully disagrees. However, without acquiescing in any way to the rejection, and solely in order to expedite allowance of the application, claim 1 has been amended to recite that the "the binding domain of the β integrin subunit for the ERK2 MAP kinase is respectively provided by the amino acid sequence KEKLKSQWNNDNPLFK (SEQ ID No. 11), RARAKWDTANNPLYK (SEQ ID No. 5), RSRARYEMASNPLYR (SEQ ID NO. 6) or RSKAKWQTGNPLYR (SEQ ID No. 4)" which is believed to render the rejection moot. Accordingly, Applicant respectfully requests withdrawal of the rejection and reconsideration.

The Examiner further rejects claims 1, 86-90, 92-99, 101, 104-106, and 108 under 35 U.S.C. § 112, 1st paragraph, as allegedly lacking enablement. Specifically,

the Examiner has stated that the specification does not enable either treatment of cancers that do not express Erk2, or the full scope of polypeptides encompassed by the aligned consensus sequences.

Applicant respectfully disagrees. However, without acquiescing in any way to the rejection, and solely in order to expedite allowance of the application, claim 1 has been amended to recite that the "ERK2 MAP kinase binds to the modified amino acid sequence and is expressed by cancer cells of the cancer…" Applicant believes that this amendment renders the rejection moot with respect to the scope of cancers that can be treated, inasmuch as the Examiner has conceded that the specification is enabled for methods of treating human cancers that express Erk2 in a mammal (Office Action, page 7). Additionally, as noted above, claim 1 has also been amended to recite that "the binding domain of the β2 integrin subunit for the ERK2 MAP kinase is KEKLKSQWNNDNPLFK (SEQ ID No. 11), RARAKWDTANNPLYK (SEQ ID No. 5), RSRARYEMASNPLYR (SEQ ID NO. 6) or RSKAKWQTGNPLYR (SEQ ID No. 4)." Accordingly, Applicant respectfully submits that modified amino acid sequences with 80% sequence identity to the selected binding domain can be readily determined by the skilled artisan. In this regard, Applicant notes that the disclosure sets out a consensus scheme derived from the alignment of the binding domains of β2, β3, β5 and β6 integrin subunits at page 18, line 27 to page 19, line 3, thereby providing detailed guidance as to amino acid changes that may be made to provide a polypeptide with a modified amino acid sequence with the requisite level of sequence identity as defined in claim 1. Accordingly, this rejection is believed to be overcome, and Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rejections Under 35 U.S.C. § 102(b)

The Examiner rejects claims 1, 86-90, 92-93, 98-99, 101, 104-106, and 108 under 35 U.S.C. § 102(b) as allegedly anticipated by Agrez (WO 2001/000677; hereinafter "Agrez"). Specifically, the Examiner has stated that Applicant's previous arguments are insufficient because there is allegedly no disclosure in Agrez requiring expression of β6 integrin on cancer cells. In support of this position, the Examiner has

pointed to Example 7 of Agrez, and related Figure 31(A), to support the position that Agrez teaches growth inhibition of non-β6 integrin expressing (-β6) SW480 colon cancer cells with a polypeptide providing the binding domain of the β6 integrin subunit (RSKAKWQTGTNPLYR) coupled to the carrier peptide penetratin.

Applicant respectfully disagrees. As noted in the previous response, Agrez does not disclose that "the β integrin is not expressed on the outer cell membrane of the cancer cells."

The Examiner has pointed to Example 7 of Agrez to support the allegation that Agrez teaches inhibition of cancer cells that do not express β integrin. However, Applicant submits that Example 7 of Agrez relates to the treatment of SW480 mock transfectant cancer cells (which do not constitutively express the β6 integrin subunit) with the RSKAWQTGTNPLYR peptide as a negative control in a study assessing the effect of the peptide on the proliferation of transfectant SW480 cells expressing β6. It is well accepted that a negative control establishes the zero base line against which results are evaluated. In other words, the test sample is compared against the negative control, and the difference between the test sample and the negative control is taken as a positive test outcome. Therefore, any inhibition of the growth of the –β6 SW480 mock transfectant cells would be viewed by the artisan of ordinary skill as an inherent artifact of the assay itself, which is ignored and subtracted from the test sample result.

In this regard, Applicant submits that Figure 29 relating to Example 6 of Agrez shows a marked inhibitory effect by penetratin alone on SW480 treated cells compared to the RSKAKWQTGTNPLYR peptide alone, reflecting the ability of penetratin to enter the cytoplasm of the cell and exert a toxic effect on the cells. Accordingly, the artisan of ordinary skill, knowing that penetratin can pass across the outer cell membrane of cells, would not ignore the toxicity exerted on the treated cells by that carrier peptide. SW480 cells are the same cell type utilized in Example 7 of Agrez. Furthermore, the discussion in Example 6 of Agrez is directed to the treatment of +β6 expressing cells and is entirely silent as to any inhibitory effect of the RSKAKWQTGTNPLYR peptide on –β6 expressing cells. As such, in view of Figure 29 showing the effect of penetratin on

SW480 cells, one of ordinary skill in the art would in fact be taught that penetratin has a toxic effect on that cell type. Moreover, the results of cell growth inhibition in Examples 6 and 8 of Agrez are reported in comparison to control cells. This is also the case in Example 7 of Agrez, where SW480 mock transfectants are treated with the RSKAKWQTGTNPLYR–penetratin complex as a comparison against SW480 transfectants expressing β6. That is, the SW480 mock transfectant cells (-β6 cells) are inherently used in the assay reported in Example 7 of Agrez as a negative control to provide the baseline with which the inhibitory effect of the peptide-penetratin complex on the +β6 SW480 transfectant cells could be evaluated. This is supported by Example 8 of Agrez which shows –β6 SW480 cells and cells expressing the β6 Δ746-764 deletion mutant (excluding the RSKAKWQTGTNPLYR fragment) being compared to SW480 cells expressing full length wild-type β6. In that Example, related Figure 32 shows essentially no growth inhibition in either the –β6 cells or the β6 Δ746-764 deletion mutant expressing cells, showing that that these cell types were being used as negative controls in the context of that disclosure.

In contrast to the Examiner's allegation that Example 7 and Figure 31(A) disclose a RSKAWQTGTNPLYR–penetratin complex inhibiting the growth of –β6 SW480 cells, the disclosure actually describes the treatment of –β6 SW480 cells as a negative control, which would be viewed as such by a person of ordinary skill in the art. Therefore, Agrez discloses the selection of a peptide providing the binding domain of a β integrin subunit that is highly expressed by target cancer cells, and does not describe target cells in which "the β integrin is not expressed on the outer cell membrane of the cancer cells." Accordingly, Agrez does not anticipate the invention. Applicant respectfully requests that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

The Examiner rejects claims 1 and 94-96 under 35 U.S.C. § 103(a) as allegedly obvious over Agrez (WO 2001/000677; hereinafter "Agrez") in view of Nadler et al. (US 5,877,282; hereinafter "Nadler"). Specifically, the Examiner stated that Nadler teaches

that a growth factor signal peptide with the amino acid sequence of AAVALLPAVLLALLA can be coupled to other polypeptides to facilitate cell entry.

Applicant respectfully traverses. As described above, Agrez does not anticipate the invention as currently claimed. Applicant respectfully submits that Nadler does not overcome any of the deficiencies of Agrez as stated above. Therefore, neither Agrez nor Nadler, alone or in combination, teach or suggest each and every element of the invention as currently claimed. Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections – Judicially Created Doctrine of Double Patenting

The Examiner has provisionally rejected claims 1, 86-90, 92-96, 98-99, 35 U.S.C. § 101, 104-106, and 108 on the grounds of non-statutory obviousness type double patenting as being unpatentable over claims 217-219, 225, 238, and 277 of co-pending U.S. Patent Application No. 10/019,816. Applicant will address the obviousness-type double patenting rejection upon a finding that the pending claims are in condition for allowance, but for the double patenting rejection.

Rejections Under 35 U.S.C. § 112, 2nd paragraph

The Examiner rejects claims 1, 86-90, 92-96, 98-99, 101, 104-106, and 108 under 35 U.S.C. § 112, 2nd paragraph, as allegedly being indefinite. Specifically, the Examiner has objected to the phrase "25 amino acids or less" with respect to the polypeptide, the phrase "or greater" with respect to the percentage of sequence identity, the term "providing" with respect to the polypeptide, and the term "incorporating" with respect to the β integrin subunit.

Applicant respectfully disagrees. However, without acquiescing in any way to the rejection, and solely in order to expedite allowance of the application, claim 1 has been amended as follows:

> A method for prophylaxis or treatment of a cancer in a mammal, comprising administering to the mammal an effective amount of a

polypeptide ~~providing~~ comprising a cytoplasmic binding domain of a β integrin subunit for ERK2 MAP kinase, or ~~having a modified amino acid sequence compared to the binding domain,~~ in which the amino acid sequence of the binding domain has been modified, the binding domain of the β integrin subunit ~~incorporating~~ having an amino acid linker region comprising amino acids that link opposite end regions of the binding domain together, the linker region being non-essential for binding of the MAP kinase to the binding domain, and the polypeptide ~~having~~ has a length of ~~25 amino acids or less~~ at least 10 amino acids, wherein the modified amino acid sequence is other than a fragment of a β integrin subunit and has 80% sequence identity with the binding domain ~~or greater~~, the ERK2 MAP kinase binds to the modified amino acid sequence and is expressed by cancer cells of the cancer, the β integrin subunit is not expressed on the outer cell membrane of the cancer cells ~~of the cancer~~, and the β integrin subunit is selected from the group consisting of β2, β3, β5 and β6, and wherein the binding domain of the β integrin subunit for the ERK2 MAP kinase is respectively provided by the amino acid sequence KEKLKSQWNNDNPLFK (SEQ ID No. 11), RARAKWDTANNPLYK (SEQ ID No. 5), RSRARYEMASNPLYR (SEQ ID NO. 6) or RSKAKWQTGNPLYR (SEQ ID No. 4).

This amendment is believed to address all of the Examiner's concerns. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

In view of the above remarks, Applicant believes the pending application is in condition for allowance. Accordingly, the Office is respectfully requested to pass this application to issue. Should any of the claims not be found to be allowable, Applicant respectfully requests the Office to telephone Applicant's undersigned representative at the number below so that a telephonic interview may be scheduled. Applicant thanks the Office in advance for this courtesy.

Dated: September 1, 2011

Respectfully submitted,

Electronic signature: /Richard B. Emmons/
Richard B. Emmons, Ph.D.
Registration No.: 68,216
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 239-0388
Attorneys/Agents For Applicant